But it was received into Parent

specification on page 7, lines 20-35 (e.g., "the major peak from the 2.HPLC eluted exactly as standard as hPTH (1-84) and co-chromatographed with hPTH (1-84) as one symmetric peak.") and page 5, lines 19-22 ("The final product is more than 95 percent pure and can be submitted directly to N-terminal amino acid sequencing, as well as amino acid composition determination"). The interpretation of "homogeneous" as used by Applicants has been accepted by the Court of Appeals for the Federal Circuit. See, *Amgen Inc. v. Genetics Institute Inc.*, 98 F.3d 1328, 1330 (Fed. Cir. 1996) ("The purity of a complex protein is described by its homogeneity, that is, the degree to which the desired protein is free of undesired proteins and other contaminants...Homogeneity may be measured by reverse phase high performance liquid chromatography (RP-HPLC), wherein movement of the composition as a single peak is an indicator of a substantially pure product."). Claims 33-35 define the hPTH (1-84) in terms of a process using a recombinant microorganism containing an exogenous DNA encoding hPTH (1-84). These claims had been pending in Applicants' copending application Serial No. 08/461,436. They are being introduced in this application simply to consolidate issues. Accordingly, no new matter has been added.

Not in Spec

Claims 27-30 have been rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite in the recitations "fully active in an adenylate cyclase assay", "intact" and "maximal response". Claim 29 was rejected on the additional ground of being inconsistent with respect to active versus passive voice.

Claims 1 and 21-30 have been canceled. New claims 31-34 do not contain these recitations. Withdrawal of the rejections are therefore requested.

Claims 1 and 21-30 have been rejected under § 102(b) as anticipated by or, in the alternative, under § 103 as obvious over Brewer et al., U.S. Patent No. 3,886,132 (the "'132 patent") for reasons of record. The Examiner has pointed out that the specification fails to define the metes and bounds of the recitation "essentially pure" and that there is no other evidence of record demonstrating a patentable difference in purity.

Applicants respectfully traverse the rejections, as they would be applied to the claims as amended, because the hPTH product disclosed in the '132 patent is not substantially homogeneous, *i.e.*, free of undesired proteins and other contaminants so as to be measured by reverse phase high performance liquid chromatography (RP-HPLC) as a single peak. The disclosure in the '132 patent is directed to the isolation and purported purification of hPTH (1-84) from human parathyroid tissue reads as follows:

> The human parathyroid hormone used in these studies was isolated from parathyroid adenomas obtained from patients undergoing surgery for hyperparathyriodism. Dried, defatted parathyroid tissue was initially extracted with 8M urea in 0.2N hydrochloric acid, and fractionated with ether, acetic acid, sodium chloride, and trichloroacetic acid (TCA powder) according to the procedure of Rasmussen et al., in J. Biol. Chem. 239, 2852-2857 (1964). The TCA powder was further purified by gel filtration, followed by ion exchange chromatography on CM-sephadex employing an ammonium acetate gradient. The isolation of the hormone was monitored by radioimmunoassay and disc gel electrophoresis.
>
> Amino acid analyses were performed on a Beckman-Spinco automatic amino acid analyzer, Model 120B or 121 adapted for high sensitivity or a Durrum Model 500 analyzer. Analytical disc gel electrophoresis was performed in 8M urea at pH 4.4 as previously reported by Brewer et al in J. Biol. Chem. 246, 5739-5742 (1970). Immunoassays were performed by the procedure of Arnaud et al in J. Clin. Invest. 50, 21-34 (1971).
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> The purified human parathyroid hormone migrated as a single component on disc gel electrophoresis with a mobility which was identical to that of the bovine parathyroid hormone. Amino terminal analysis of the purified peptide by the Edman technique revealed serine.

The '132 patent at column 1, line 68 through column 2, lines 1-22; column 2, lines 49-54. The Declaration by Dr. Maggio sets forth the opinion that the combination of gel filtration and ion exchange chromatography did not achieve an essentially pure (i.e., substantially homogeneous) hPTH(1-84). The relevant portion of Paragraph 9 of the Declaration reads as follows:

> Moreover, two later publications cited by Dr. Spector in the Official Action, namely *Kimura et al.* and *Kumagaye et al.*, show that the purification protocols discussed in *Brewer et al.* result in impure materials. For example, Fig. 2, on page 496 of *Kimura et al.* is an HPLC profile of crude product obtained after use of a separation protocol analogous to that disclosed in *Brewer et al.*; namely, the use of a combination of gel filtration and ion exchange chromatography. Impurities are plainly evident. Therefore, a conclusion of homogeneity based on *Brewer et al.* is unjustified. Further, *Kimura et al.* describe a purification sequence of CM-cellulose column chromatography followed by gel filtration on Sephadex G-50, followed in turn by the use of reverse phase-high pressure liquid chromatography ("RP-HPLC"). *Kimura et al.* added the RP-HPLC step in recognition of the need to obtain better

> purity than *Brewer et al.* obtained. This fact alone, in my opinion, eliminates any plausible basis for concluding that the protein resulting from the methods described in *Brewer et al.* was essentialiy pure.

In response, the Examiner argued:

> At pages 5-6 of the Amendment, Applicants argue that the protein of *Brewer et al.* can not have been pure enough to meet the limitations of the claims, in view of the previous arguments of the Kimura, Fairwell, and Kumagaye references. This argument has been fully considered but is not deemed persuasive. The Kimura, Fairwell, and Kumagaye references are not analogous to Brewer, as they relate to purification of synthetic hPTH, as opposed to Brewer's isolation of naturally occurring hormone. The ordinary artisan would immediately recognize that the nature of the impurities in a natural preparation would be substantively different from those obtained in an *in vitro* peptide synthesis. Whereas in an *in vitro* synthesis would yield an initially heterogeneous mix of a variety of closely related products (having terminated at different steps of the synthesis of being differentially derivatized), one would not expect such a mix of closely related species in a preparation obtained from the natural source. It is further noted that Fig. 2 of Kimura, to which Applicants refer, is an HPLC chromatogram of the crude product obtained from peptide synthesis, and has no bearing on the naturally occurring product.

Paragraphs bridging pages 5-6 of the Official Action, mailed January 13, 1997.

However, the Examiner's assumption of purity is unwarranted. As the documents submitted in the accompanying IDS establish, (one of the submitted articles is from Brewer's group) isolating a specific peptide from natural sources such as a gland is very difficult. To assume that a greater level of purity is achieved when isolating hPTH from a gland merely because the types of starting material are different and that the types of probable contaminants resulting are different is not justified on this record.

Recall that Brewer's group never intended to provide a level of purity as described and claimed in this application. They only sought sufficiently pure glandular hPTH to allow for sequencing; his true objective. This is consistent with statements Brewer's group made, (*See* '132 patent at Col. 1, lns. 59-65), as well as the realities of the difficulties faced by Brewer's group. As the Brewer article makes clear, the effort necessary to collect sufficient glandular material was enormous. An "international cooperative effort" of "[m]ore than 150 individual laboratories, physicians, surgeons, and

pathologists donated human parathyroid tissue... ." The yield, after purification was probably less than a milligram. Since the objective was sequencing, additional losses due to exhaustive purification would have been unwarranted. Homogeneity is not needed for sequencing.

Perhaps most importantly, however, Brewer's group failed to meet their own objective because they were not even able to purify their hPTH sample sufficiently to allow for proper sequencing. The lack of purity of Brewer's material is clear from, *inter alia*, Fig. 3 of the Brewer paper which illustrates the sequencing cycles of the N-terminal region of hPTH. In Fig. 3, several of the sequencing cycles illustrate more than one significant peak. The most likely explanation for the presence of such peaks, other than incompetence or equipment malfunction, is the presence of "sequenceable impurities." Moreover, as the relative peak heights of these additional peaks often approaches that of the peaks attributed by Brewer's group to the actual amino acids in the sequence, one must conclude that the relative concentration of those sequenceable impurities rivals the concentration of hPTH in the sample. The ambiguity that these levels of sequenceable contaminants caused is the significant factor in Brewer's inability to properly identify the amino acids in positions 22, 28 and 30. The fact that impurities of this level also appear in other cycles only serves to verify this conclusion. For example, additional peaks in cycles 2, 10, 12, 21, 24, 26 and 29 also suggest significant sequenceable impurities.[1]

These errors and therefore the lack of purity achieved by Brewer's group were recognized by others very quickly. In 1974, a paper written by Niall et al. reexamined the sequencing determinations of Brewers group. *See* Niall et al., *PNAS* 71:384-388, Feb. 1974. A copy of the Niall et al. paper is included with and is identified in the concurrently filed IDS. Niall's group had previously examined the N-terminal fragment of hPTH and had reached a different conclusion than Brewer's group as to its sequence. This paper, and another by the same group, Keutmann et al., (*See* the concurrently filed IDS) reports their own reexamination of their prior work as well as that of Brewer's group. Niall's group concluded that Brewer was wrong in the three positions along the sequence previously identified.

One of ordinary skill in the art could not read the Brewer paper, the '132 patent and the Niall et al. paper and conclude that the '132 patent had obtained hPTH of a

[1] Moreover, this type of analysis only reveals "sequenceable impurities" and does address the presence of other impurities, such as amino-terminally blocked peptides or non-peptide components such as sugars or lipids sure to be present in a gland.

purity even approaching that achieved by the inventors.[2] In fact, even with more definitive testing and a much better description of analytical methods, Niall still conceded that "[u]ltimate resolution of the differences in the proposed structures must await further study." *Id.* at 387.

Ample evidence of the superiority of the purity of the claimed invention over the '132 patent is of record. Therefor, the rejection over the '132 patent should be withdrawn and the application passed to issue. Should the Examiner have any questions with regard to the foregoing, the Examiner should contact the undersigned, at the Examiner's convenience, at (908) 654-5000. Furthermore, should any fee be due and owing in this regard, the Examiner should charge Deposit Account No. 12-1095 therefor.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

Respectfully submitted,

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[2] The Niall group report achieving purity levels which those of skill in the art will readily recognize to be superior to Brewer but inferior to those achieved by the present invention. When the Niall group speaks of purity, the do so in the same context as Brewer. That is to say purity is based on the presence of absence of "sequencable impurities." That is not equivalent to homogeneity as presently claimed.